PSYCHOPHARMACOLOGY RESOURCE NETWORK (PRN)
ROLE IN
DIVERSION

Juan Carlos Arguello, DO
Assistant Deputy Director Clinical Operations
Chief, Office of Medical and Psychiatric Services

THE ORIGINS OF PRN

DSH PATIENT PROFILE:

- Vulnerable
- Severe Mental Illness (Schizophrenia, schizoaffective Disorder, Bipolar Disorder)
- Involved in Criminal Justice
- Medication Resistant
- Multiple medications trial
- Still having significant symptoms
- Aggression
- Cognitive problems
- Also major medical illnesses

THE BIRTH OF PRN:

1994- Dr. Michael Cummings,
"The Army of One".
Patton State Hospital

2012- Drs. Stephen Stahl and Kate Warburton
" The Visionaries"

Dr. Laura Dardashti leadership
2013- PRN Group Expansion

Dr. J.C. Arguello joined 2017

CURRENT PSYCHOPHARMACOLOGY RESOURCE NETWORK TEAM

Dr. Stephen Stahl
DSH Director of Pharmacology Services

Dr. Michael Cummings

Dr. George Proctor

Dr. Jennifer O'Day

Dr. Eric Schwartz

Dr. Jonathan Meyer

Dr. Aili Arias

PRN STRATEGIES

TREATMENT AS USUAL (TAU) OR NEW APPROACH

CLOZAPINE

STRATEGIC MEDICATION COMBINATION

OBTAINING ANTIPSYCHOTIC DRUG LEVELS TO GUIDE MEDICATION TREATMENT

USING LONG ACTING INJECTABLE (LAI) MEDICATION

TOTAL PRN CONSULTATIONS IN 2018

5,067

PRN COMMITTEE REPRESENTATION

- **Psychopharmacology Advisory Committee (PAC)** – Eric Schwartz, M.D. serves as Co-Chair and Michael Cummings, M.D. This committee manages revision and publication of Policy Directive 3400 and the appended DSH Psychotropic Medication Policy.

- **Common Drug Formulary Committee (CDFC)** -- Michael Cummings, M.D. and Jennifer O'Day, M.D. serve as members of this Department of General Services (DGS) Committee. This committee manages the Common Drug Formulary and participates in guiding DGS with respect to negotiation of pharmacology contracts.

- **Continuing Medical Education Committee (CME)** – Jonathan Meyer, M.D. coordinates scheduling and facilitating the ongoing CME lecture series for both psychopharmacology and forensic topics. Weekly to all hospitals and CDCR

- Dr. Cummings serves on the **DSH-Patton Clinical Management Committee**. He previously served as vice-chair of the DSH-Patton Pharmacy & Therapeutics Committee.

- Jennifer O'Day, M.D. has served at DSH-Metropolitan as both **Chair of the Department of Psychiatry** and previously as **Chair of the Pharmacy & Therapeutics Committee**.

- George Proctor, M.D. serves at DSH-Patton as **Chair of the Pharmacy & Therapeutics Committee**, as well as on the **By-Laws Committee**.

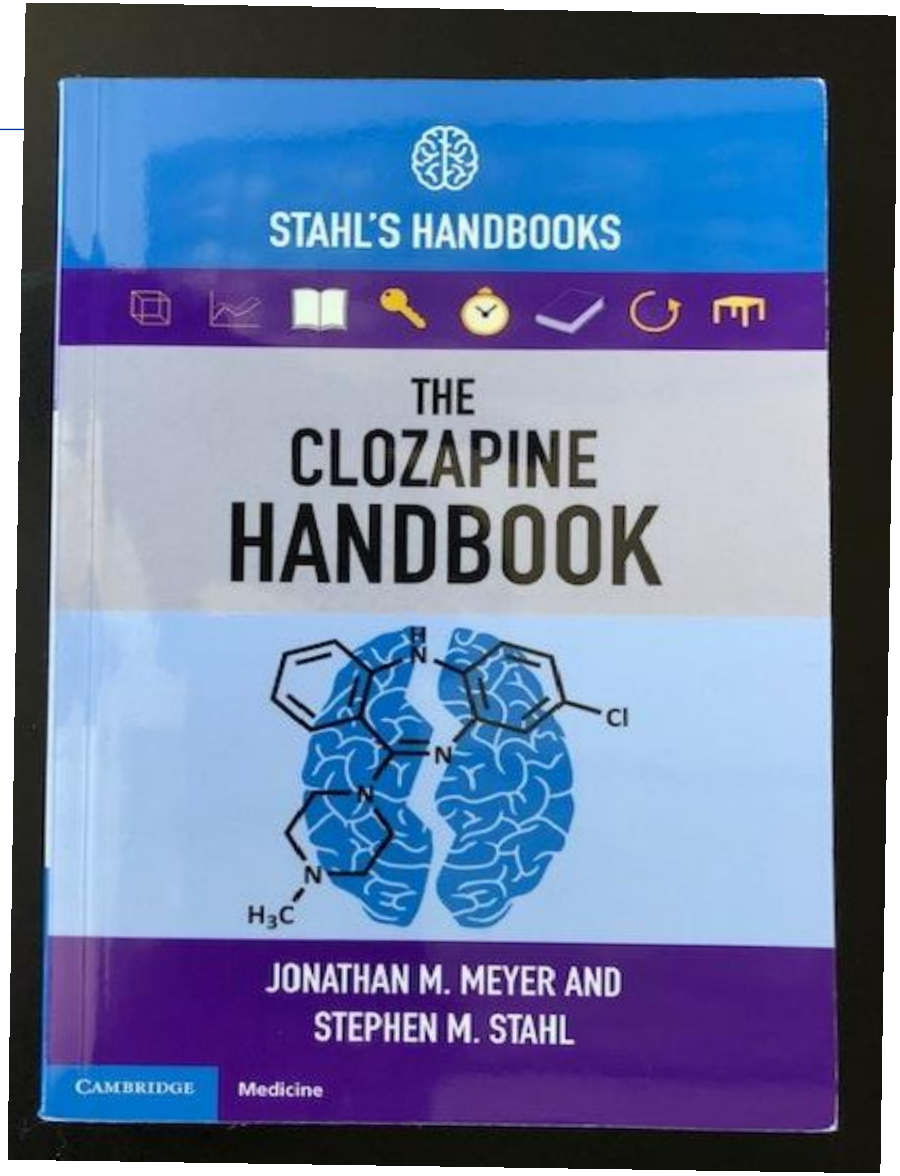
PRN PUBLICATIONS SAMPLE

- Stahl SM. Deconstructing violence as a medical syndrome: mapping psychotic, impulsive and predatory subtypes to brain circuits. CNS Spectrums 2014; 19:357-365.
- Stahl, SM et all. California state hospital violence assessment and treatment (CAL-VAT) guidelines. CNS Spectrums 2014;19:449-465.
- Morussette DA, Stahl SM. Treating the violent patient with psychosis or impulsivity utilizing antipsychotic polypharmacy and high dose monotherapy. CNS Spectrums 2014; 19:439-448.
- O'Day J, Dardashti L, Delgado D, Schwartz, E, Broderick C, Stahl, S. (2014). Genetics and Epigenetics of Mental Illness: Implications for Diagnosis and Treatment. Wiley Encyclopedia of Forensic Sciences, 1-9.
- Warburton KD, Stahl SM. Treat the treatable: a comprehensive and optimistic approach to treat psychotic violence. CNS Spectrum 2015;03:170-171.
- Stahl SM. Is impulsive violence an addiction? The habit hypothesis. CNS Spectrums 2015;3:165-169.
- Meyer JM, Proctor GJ, Cummings MA, Dardashti, L. Case report: ciprofloxacin and clozapine: a potentially fatal but underappreciated interaction. Hindawi 2016.
- Meyer JM, Cummings MA, Proctor GJ, and Stahl SM. Psychopharmacology of persisting violence and aggression. Psychiatr Clin North Am 2016 Dec; 39(4): 541-55
- McDermott BE, Newman W, Scott CL, Meyer JM, Warburton KD. The utility of an admission screening procedure for patients committed to a state hospital as incompetent to stand trial. International Journal of Forensic Mental Health 2017;16:281-92.
- Meyer JM. Deutetrabenazine for tardive dyskinesia. Current Psychiatry 2017;16:35-41.
- Meyer JM. Valbenazine for tardive dyskinesia. Current Psychiatry 2017;16:40-6.
- Meyer JM. A concise guide to monoamine oxidase inhibitors: part 1. Current Psychiatry 2017;16:14-6.

PUBLICATION CONTINUATION

- Meyer JM. Converting oral to long acting injectable antipsychotics: a guide for the perplexed. CNS Spectrums 2017;22:14-28.
- Meyer JM, Cummings MA, Proctor G. Augmentation of phenelzine with aripiprazole and quetiapine in a treatment-resistant patient with psychotic unipolar depression: case report and literature review. CNS Spectrums 2017;22:391-6.
- Meyer JM, Ng-Mak DS, Chuang C-C, Rajagopalan K, Loebel AD. Weight changes before and after lurasidone treatment: A real-world analysis using electronic health records. Annals of General Psychiatry 2017;16:36.
- Moore BA, Morrissette DA, Meyer JM, Stahl SM. "Unconventional" treatment strategies for schizophrenia: polypharmacy and heroic dosing. BJPsych Bulletin 2017;41:164-8.
- Cummings MA, Proctor GJ, Stahl SM. Deutetrabenazine for Tardive Dyskinesia (New Drug REview). Clin Schizophr Relat Psychoses 2018 Jan; 11(4): 214-220.
- Black KJ, Nasrallah H, Isaacson S, et al. Guidance for switching from off-label antipsychotics to pimavanserin for Parkinson's Disease Psychosis: an expert consensus. CNS Spectrums 2018; *in press*.
- Meyer JM. Pharmacotherapy of Psychosis and Mania. In: Brunton LL, Hilal-Dandan R, Knollmann BC, eds.
- Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th Edition. Chicago, Illinois: McGraw-Hill; 2018:279-302.

American Psychiatric Association Annual Meeting in San Diego 2016
PRN presentation on clozapine standing room only


STAHL'S HANDBOOKS
THE
CLOZAPINE
HANDBOOK
JONATHAN M. MEYER AND
STEPHEN M. STAHL
CAMBRIDGE
Medicine

PRN AND DIVERSION

PARTNERING WITH DIVERSION PROGRAM PARTICIPATING COUNTIES:

- Evaluate the best medication approach for the diverted patient population
- Provide trainings
- Consultation on difficult patients
- Develop guidelines for the treatment of diverted patients

PRN ARTICLES AND BOOKS PENDING PUBLICATION

- Monitoring and Improving Antipsychotic Adherence in Outpatient Forensic Diversion Programs by Dr. Jonathan Meyer
- Dopamine Antagonist Antipsychotics in Diverted Forensic Populations by Drs. Cummings, Proctor, and Arias
- Beyond the Guidelines: Management of Complex, Treatment resistant psychotic disorders, a handbook for forensic/state hospitals by Drs. Cummings and Stahl

THE SUCCESS OF THE DSH PRN MODEL

EXPANSION OUTSIDE DSH

- CDCR – Dr. Joan Striebel trained by DSH PRN
- Australian State Hospitals planning PRN team
- United Kingdom Forensic Hospitals

UNIQUE ASPECTS OF PSYCHOPHARMACOLOGY FOR THE DIVERSION POPULATION

Chair: Stephen M. Stahl, MD, PhD

Director of Psychopharmacology Services– California DSH

Adjunct Professor, Department of Psychiatry,

University of California, San Diego

Honorary Fellow, Department of Psychiatry, University of Cambridge

Co-chair: Jonathan M. Meyer, MD

Psychopharmacology Consultant – California DSH

Clinical Professor, Department of Psychiatry,

University of California, San Diego

OUR DIVERSION CLIENT

25 year old WM with h/o schizophrenia since age 21, and substance use disorders (cannabis, methamphetamine). From out of state, no local family, intermittently homeless. Prior arrests for petty theft, public intoxication, drug possession. Several psych hospitalizations.

- **Charge: Calif PC 422 (criminal threats)**
  - **Offense:** threatened a random individual at a trolley station with 'dismemberment' for seemingly psychotic reasons. Was agitated at time of arrest, and urine tox was positive for amphetamines and THC.
  - **Treatment in jail:** after receiving several emergency IM PRN doses he agreed to an oral antipsychotic. Has responded and is now interested in diversion to avoid legal consequences.

OBJECTIVES

- **Diversion participants have high rates of schizophrenia, a diagnosis associated with nonadherence**
  - substance use comorbidity increases this risk
- **Management of nonadherence is critical in diversion programs**
  - pill counts, use of plasma antipsychotic levels and long-acting injectable antipsychotics
- **Other aspects of treatment**
  - implementation of clozapine for treatment resistant patients
  - use of antipsychotic concentrates, dissolving tablets (e.g. asenapine), and possibly other options (inhaled loxapine, olanzapine) to manage exacerbations and forestall psychiatric admission and re-offense.

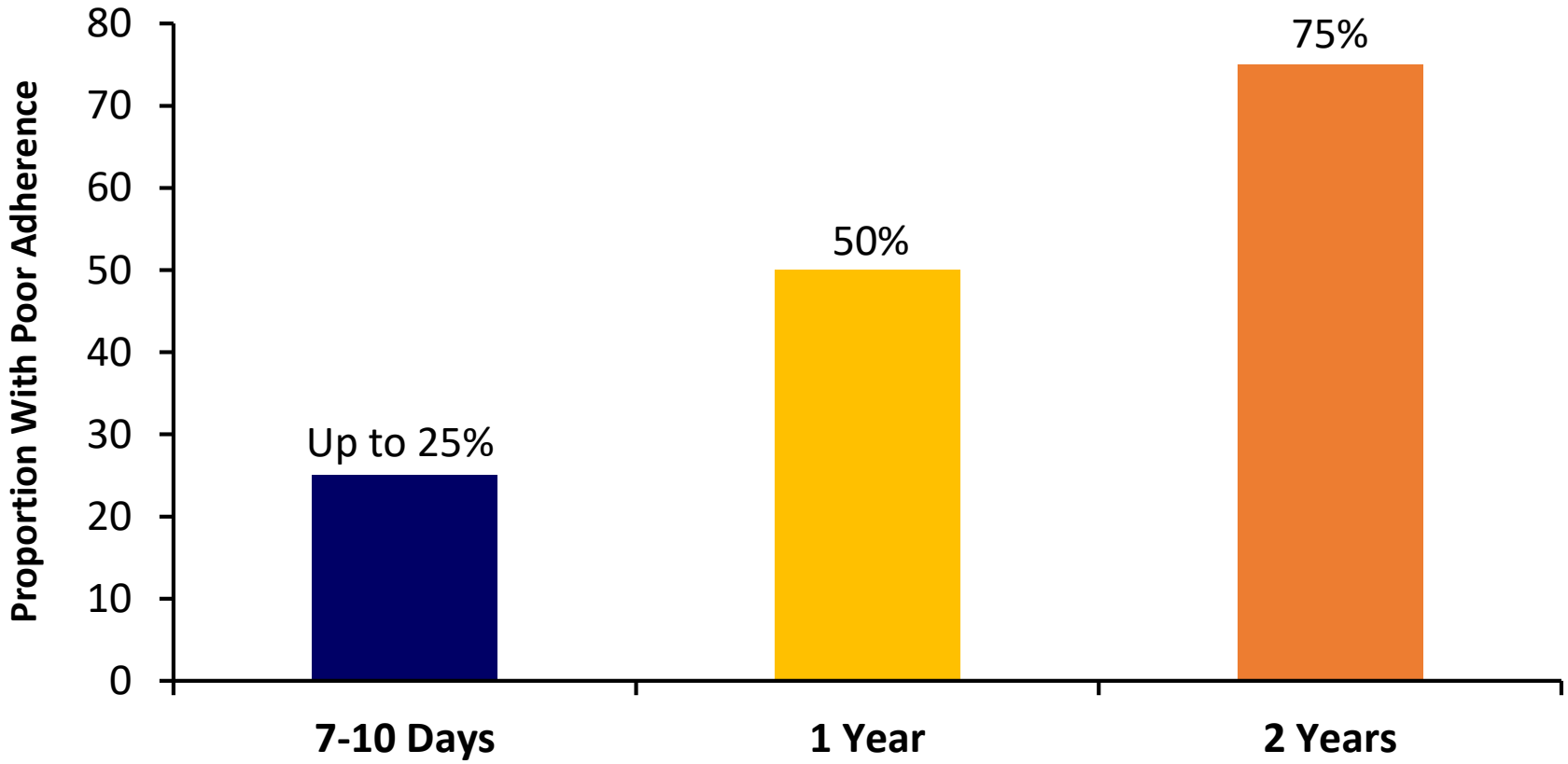
Adherence

ANTIPSYCHOTIC ADHERENCE FACTS

- Antipsychotic nonadherence is common to all chronic illnesses, with 50% incidence noted in multiple studies of schizophrenia patients
- Predictors of nonadherence: medication adverse effects, lack of insight, poor social support, substance use
  - Independent predictor: **attitude towards antipsychotic treatment**

1. Dufort A, Zipursky RB. Understanding and managing treatment adherence in schizophrenia. *Clin Schizophr Relat Psychoses. 2019; in press*
2. Meyer JM. Monitoring and Improving Antipsychotic Adherence in Outpatient Forensic Diversion Programs. *CNS Spectrums 2019; in press*

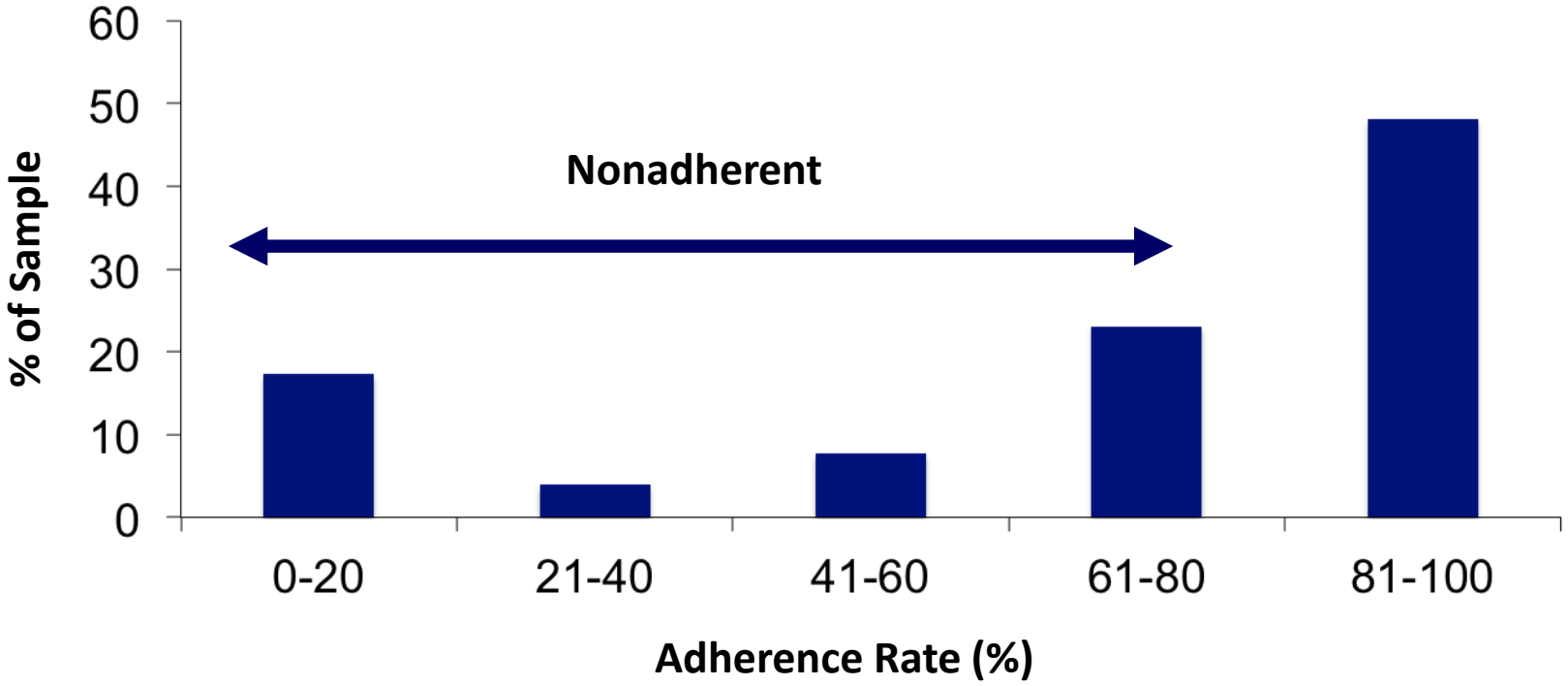
TIME COURSE OF POOR ADHERENCE SINCE ANTIPSYCHOTIC INITIATION



Keith SJ, Kane JM. *J Clin Psychiatry.* 2003;64(11):1308-1315.

THE RANGE OF ADHERENCE IN SCHIZOPHRENIA

4-week MEMSCap data on 52 outpatients with schizophrenia in ***an adherence study*** reveal patterns of nonadherence

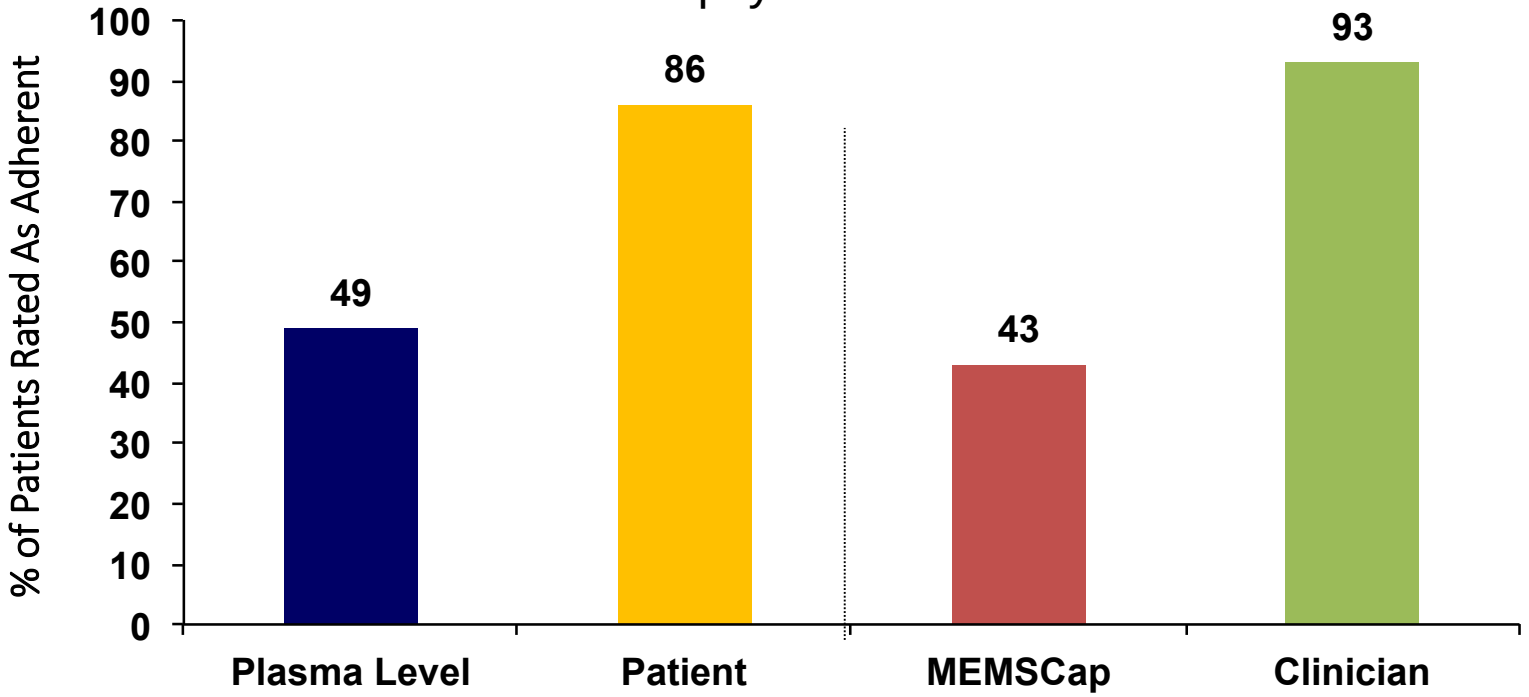


MEMSCap = Medication Event Monitoring System.

Remington G, et al. *J Clin Psychopharmacol*. 2013;33(2):261-263.

ACCURATE ASSESSMENT OF ADHERENCE IS DIFFICULT FOR PATIENTS & CLINICIANS

Two separate studies found that both patients* and clinicians† overestimate antipsychotic adherence



MEMSCap = Medication Event Monitoring System

*Criterion: "took all pills." † Criteria: > 70% of pills; score > 4 on clinician rating scale.

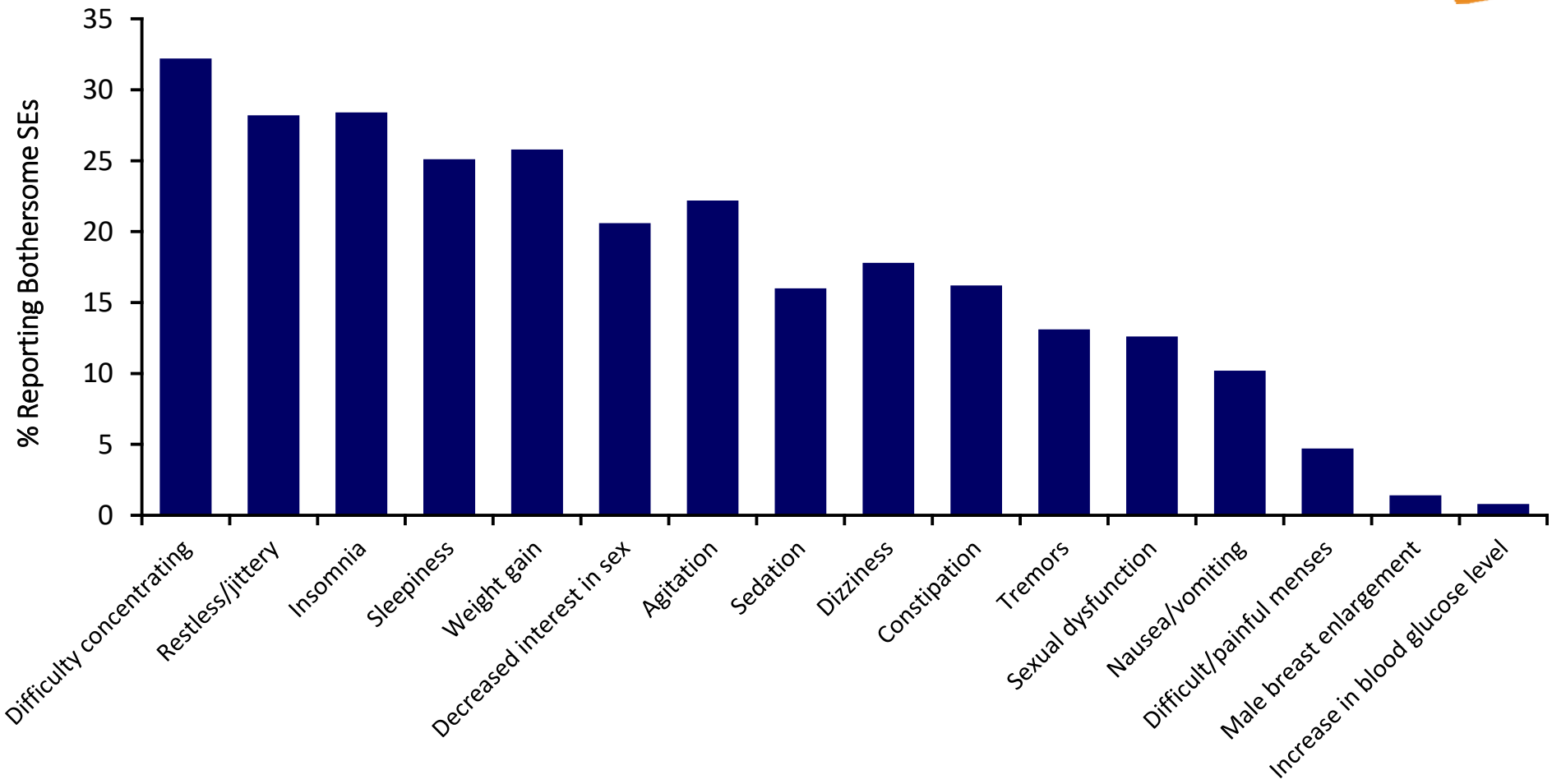
*Velligan DI, et al. *Psychiatr Serv*. 2007;58(9):1187-1192. †Byerly M, et al. *Psychiatr Serv*. 2007;58(6):844–847.

FORENSIC CONSEQUENCES OF NONADHERENCE

- Among 63 NGI prison parolees with schizophrenia, poor adherence to treatment increased the odds of reoffense 10-fold (OR=10.42; p=0.001).[1]
- In a Canadian study of 11,462 offenders with schizophrenia and mean follow-up of 10 yrs, lower antipsychotic adherence levels were significantly associated with increased adjusted risk ratios (ARR) of reoffense compared to those with high adherence rates (≥ 80%):
  - **violent offenses** (***ARR = 1.58***; 95% CI = 1.46-1.71)
  - **nonviolent offenses** (***ARR = 1.41***; 95% CI = 1.33-1.50)

1. Oueslati, B, Fekih-Romdhane, F, Mrabet, A, et al. Correlates of offense recidivism in patients with schizophrenia. Int J Law Psychiatry. 2018; 58178-183.
2. Rezansoff, SN, Moniruzzaman, A, Fazel, S, et al. Adherence to Antipsychotic Medication and Criminal Recidivism in a Canadian Provincial Offender Population. Schizophr Bull. 2017; 43(5): 1002-1010.

ADVERSE EFFECTS ASSOCIATED WITH DECREASED ANTIPSYCHOTIC ADHERENCE (N=876)



DiBonaventura M et al. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry 2012;12:20.

ADVERSE EFFECTS ARE ASSOCIATED WITH DECREASED ANTIPSYCHOTIC ADHERENCE (N=876)

Most side effects were associated with a significantly reduced likelihood of adherence. When grouped as side-effect clusters in a single model (**OR** = odds ratio):

- **extrapyramidal symptoms/agitation** (OR 0.57, p=0.0007)
- **sedation/cognition** (OR 0.70, p=0.033)
- **prolactin/endocrine** (OR 0.69, p=0.0342)
- **metabolic side effects** (OR 0.64, p=0.0079)

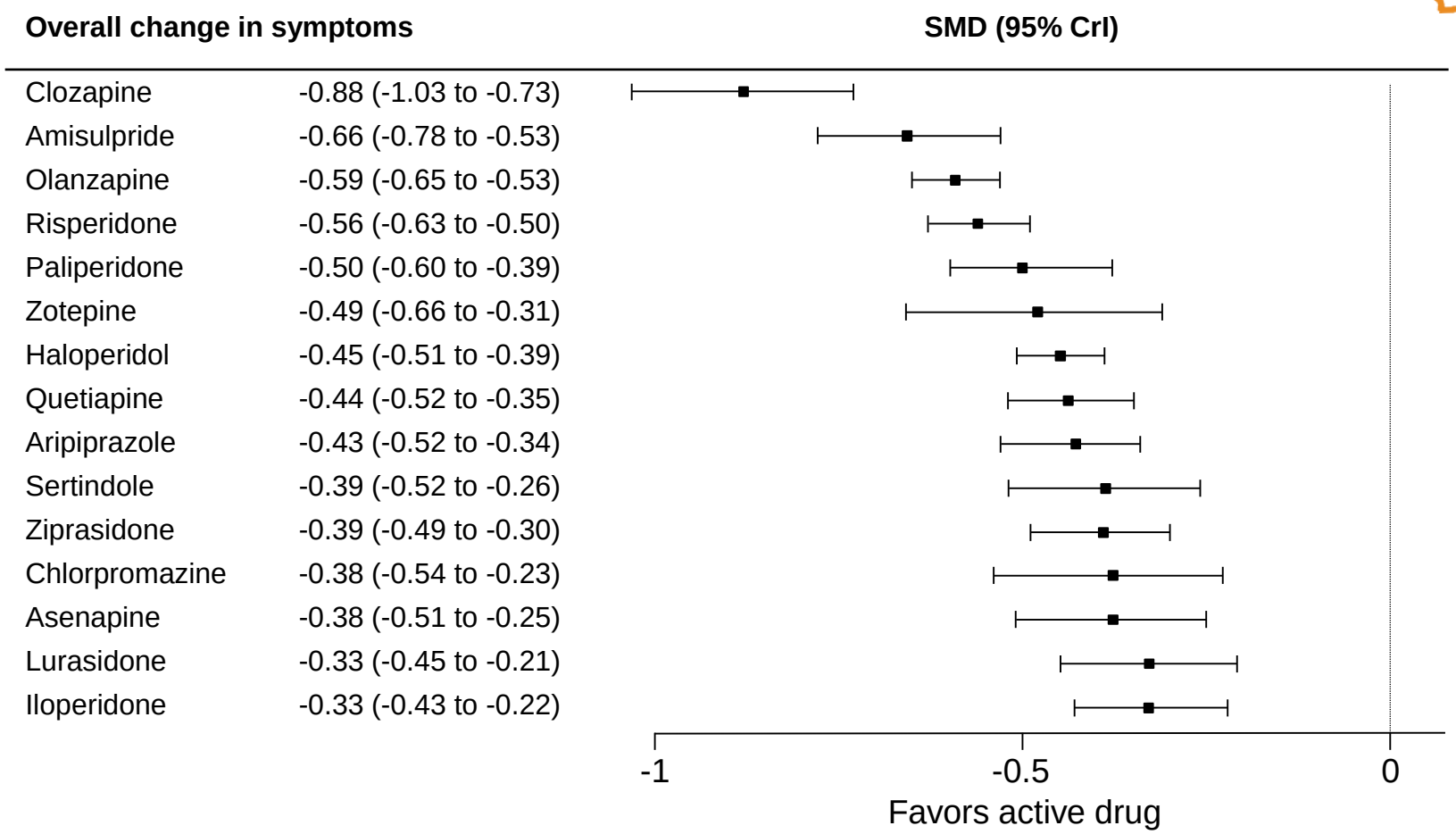
were all significantly related to lower rates of adherence

DiBonaventura M et al. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry 2012;12:20.

ANTIPSYCHOTIC CHOICE: CONCEPTS

- Among schizophrenia patients who are not treatment resistant, all agents have comparable effectiveness.
- Medication choice is driven more by:
  - avoidance of adverse effects
  - route of delivery
- For treatment resistant schizophrenia patients, clozapine is the only effective medication.

ANTIPSYCHOTIC EFFICACY VS PLACEBO



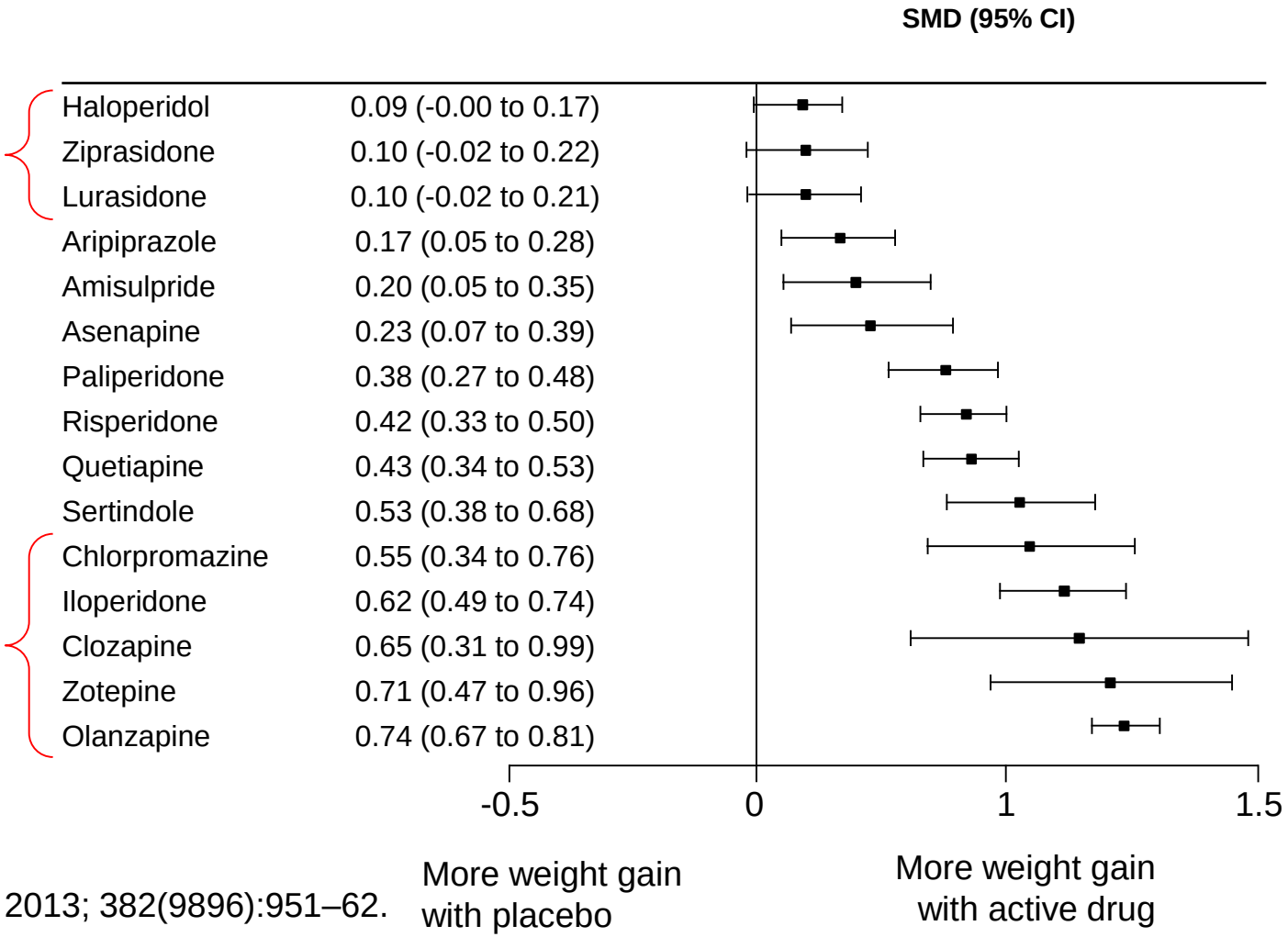
'….the differences in efficacy between drugs were small (standardized mean differences 0.11–0.55, median 0.24)'

Leucht S, *et al.* Lancet. 2013; 382(9896):951–62.

ANTIPSYCHOTIC WEIGHT GAIN VS PLACEBO

No significant difference in weight gain vs placebo

5 drugs with most weight gain vs placebo



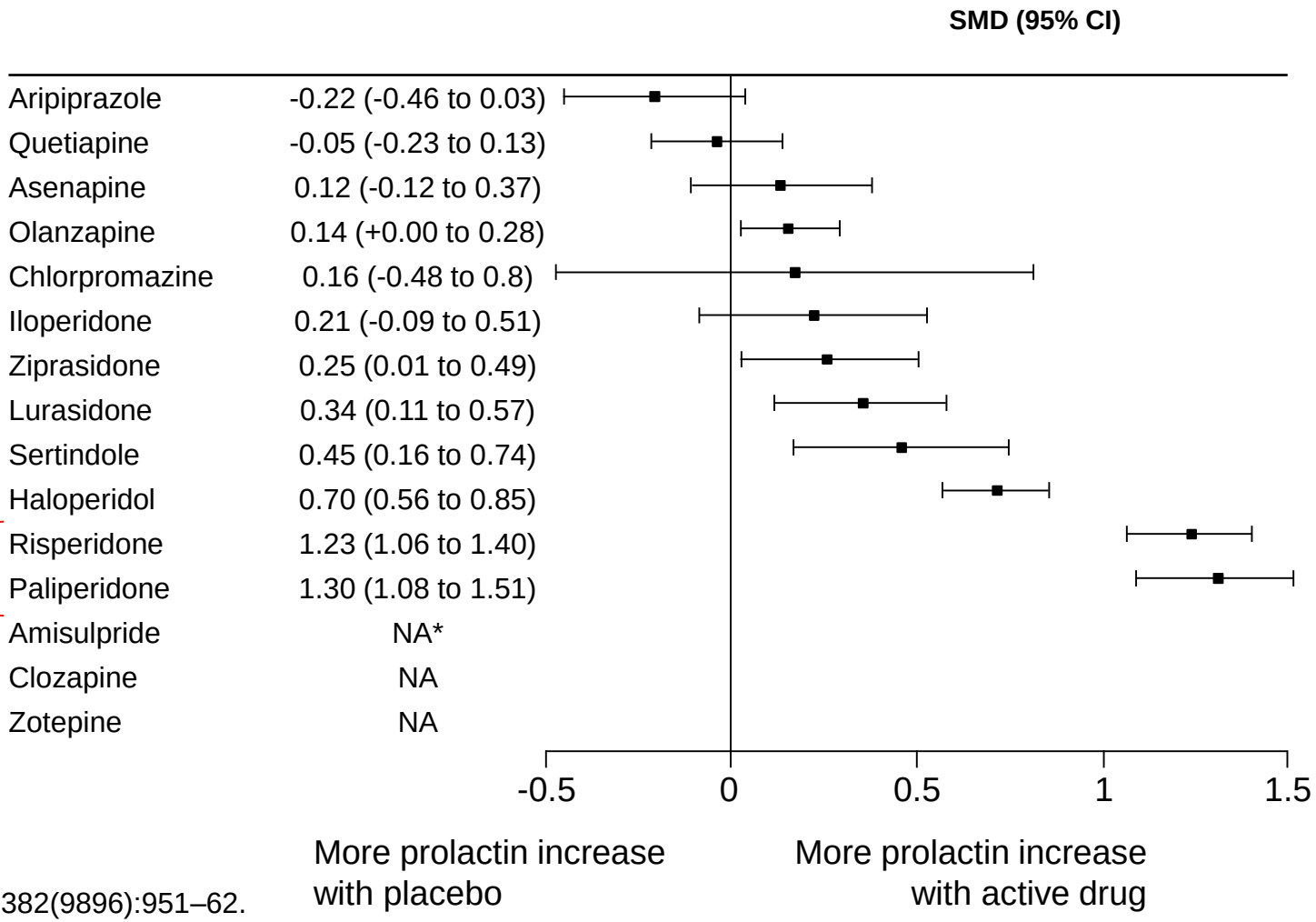
Leucht S, *et al.* Lancet. 2013; 382(9896):951–62.

METABOLIC IMPACT OF NEWER ANTIPSYCHOTICS

Drug	Weight Gain	Risk for Type 2 DM	Worsening Lipid Profile
Clozapine	+++	+++	+++
Olanzapine	+++	+++	+++
Quetiapine	+++/++	++	++
Risperidone	++	++/+	++/+
Paliperidone	++	++/+	++/+
Asenapine	+	+	+
Iloperidone	+	+	+
Brexpiprazole	+	+/-	+/-
Aripiprazole	+/-	+/-	+/-
Ziprasidone	+/-	+/-	+/-
Lurasidone	+/-	+/-	+/-
Cariprazine	+/-	+/-	+/-

Yogaratnam J, et al. **Metabolic Complications of Schizophrenia and Antipsychotic Medications — An Updated Review.** East Asian Arch Psychiatry 2013;23:21-8

ANTIPSYCHOTICS & PROLACTIN INCREASE VS PLACEBO



Most marked effect

Leucht S, *et al.* Lancet. 2013; 382(9896):951–62.

Using Plasma Antipsychotic Levels

OUR DIVERSION CLIENT – PART 2

Events:

- Our client was stabilized on risperidone 4 mg qhs in jail, and improved significantly. He understood the diversion program guidelines and was eventually transitioned to unlocked but 'supervised' community housing that administers his medication.
- Weekly urine drug screening has been negative, but after 6 weeks in the placement our client is appearing a bit disorganized, occasionally verbally hostile, though apologetic. The staff indicate that he is cooperative with his medication (unlike some other residents).

OUR CLIENT HAS RELAPSED: LIKELY CAUSE?

1. Medication nonadherence
2. Medication nonadherence
3. Medication nonadherence
4. Medication nonadherence
5. Substance use
6. Psychosocial stressors
7. Medical illness
8. Illness fluctuation

IS MY CLIENT TAKING HIS RISPERIDONE?

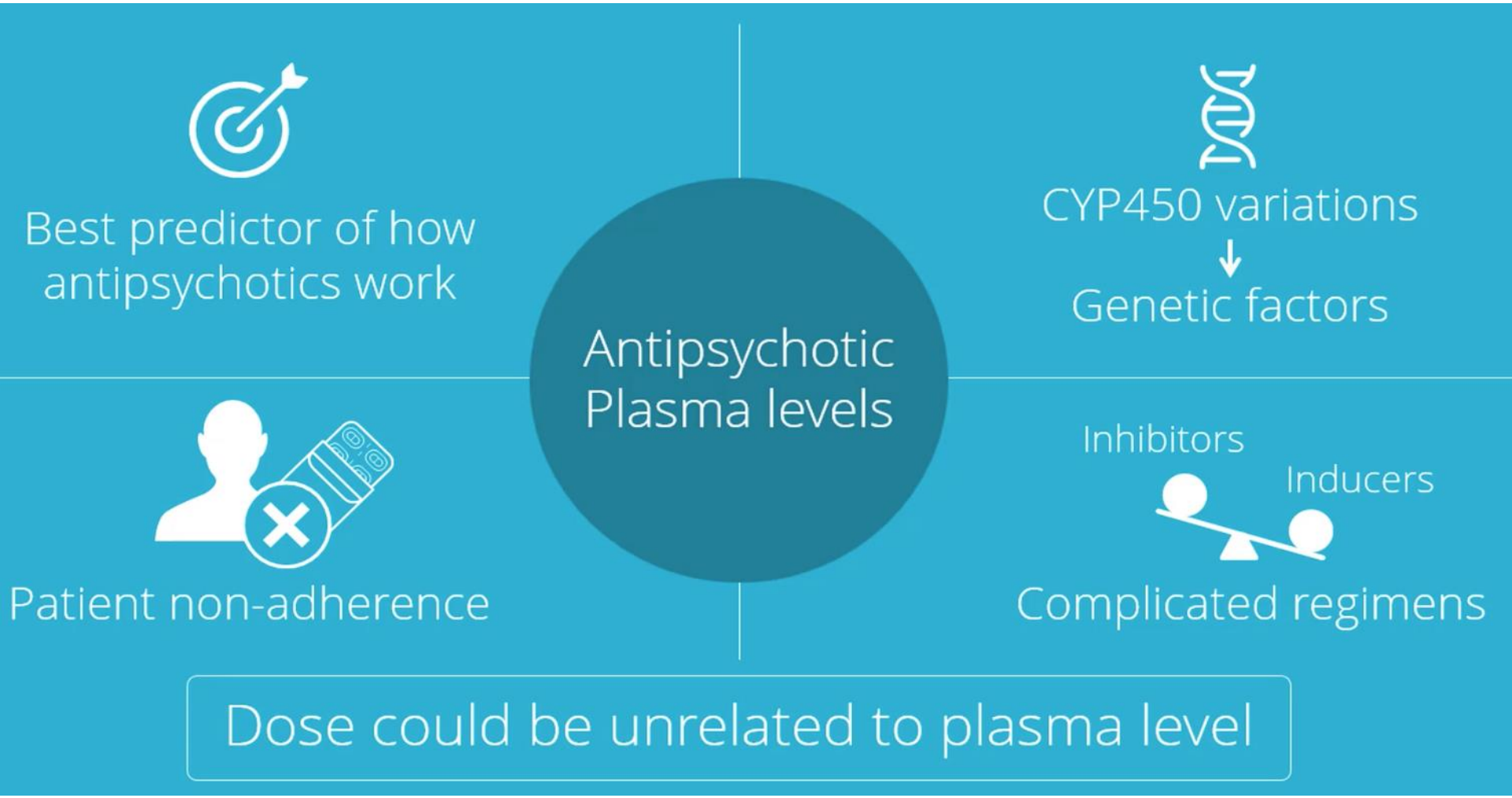
- For patients who self-administer oral medication, weekly pill counts are an evidence based method to track adherence. [1]
- When oral meds are overseen by clinical staff, plasma drug levels are the only method to determine if a patient is cheeking. [2]

Suspicious of medication nonadherence with oral risperidone, the diversion program psychiatrist orders a morning risperidone level.

Question: What level is expected based on the dose?

1. Velligan DI, et al. Relationships Among Subjective and Objective Measures of Adherence to Oral Antipsychotic Medications. Psychiatric Services 2007; 58: 1187-92.
2. Meyer JM, et al. Psychopharmacology of Persistent Violence and Aggression. Psych Clin N Am 2016; 39(4) 541-556.

CONCEPTS: ANTIPSYCHOTIC PLASMA LEVELS



CONCEPTS – PLASMA ANTIPSYCHOTIC LEVELS

1. The best proxy for what is happening in the brain
2. Can be used to track oral medication adherence
3. Very useful when patients fail to respond to 'usual' therapeutic antipsychotic dosages.
   - Helps separate true treatment resistant from those who just have low drug levels due to nonadherence or genetic variants in drug metabolism
   - Important when deciding when to call it quits and start clozapine for treatment resistant schizophrenia

Oral Dose-Plasma Level Relationships

Medication	Relationship (Concentration in ng/mL)		
Fluphenazine	**Very limited data available.**		
Olanzapine	**Concentration:** **Concentration:**	2.00 x oral dose (mg/d) 1.43 x oral dose (mg/d)	(nonsmokers) (smokers)
Perphenazine	**Concentration:** **Concentration:**	0.08 x oral dose (mg/d) 0.04 x oral dose (mg/d)	(2D6 PM) (2D6 EM)
Risperidone	**MR:** Risperidone/9-OH Risperidone: 0.2 (range 0.1 – 0.3) **Concentration (risperidone + 9-OH risp):** 7.0 x oral dose (mg/d)		

MR = metabolic ratio

Meyer JM, et al. Psychopharmacology of Persistent Violence and Aggression. *Psych Clin N Am 2016;* 39(4):541-556.
Linnet K, Wiborg O. Steady-state serum concentrations of the neuroleptic perphenazine in relation to CYP2D6 genetic polymorphism. Clin Pharmacol Ther 1996;60:41-7.

WHAT RISPERIDONE LEVELS DO I EXPECT ON 4 MG QHS?

The 12-hr trough levels expected for this patient are:

- Risperidone: 4.5 ng/ml
- 9-OH risperidone: 23.5 ng/ml
- Total (active moiety): 28 ng/ml (7.0 x the oral dose)

Also, the ratio of risperidone to 9-OH risperidone should be around 0.2 (range 0.1 – 0.3) in those who metabolize the drug normally. For the above result this ratio is **0.19.**

PRACTICAL CONSIDERATIONS – ANTIPSYCHOTIC PLASMA LEVELS

- Plasma levels on oral meds should be obtained in the morning approximately 12 hrs after the bedtime dose.
- Even among adherent patients, levels may fluctuate up to 30%. Changes beyond this (when replicated) are usually due to nonadherence or a new kinetic issue. [1]

1. Meyer JM. Is monitoring of plasma antipsychotic levels useful? Current Psychiatry. 2015; 14(11): 16:19-20

OUR DIVERSION CLIENT – PART 2

Lab results (drawn 12 hours after his evening dose):

- Risperidone: 2.0 ng/ml
- 9-OH risperidone: 10.0 ng/ml
- Total (active moiety): 12 ng/ml (only **3.0** x the oral dose)
  - He metabolizes risperidone normally since the metabolic ratio is exactly 0.2.

Our client appears to be nonadherent and is presented with the lab results. He promises to do better and a repeat plasma level is planned in 2 weeks, but the client is not told the date.

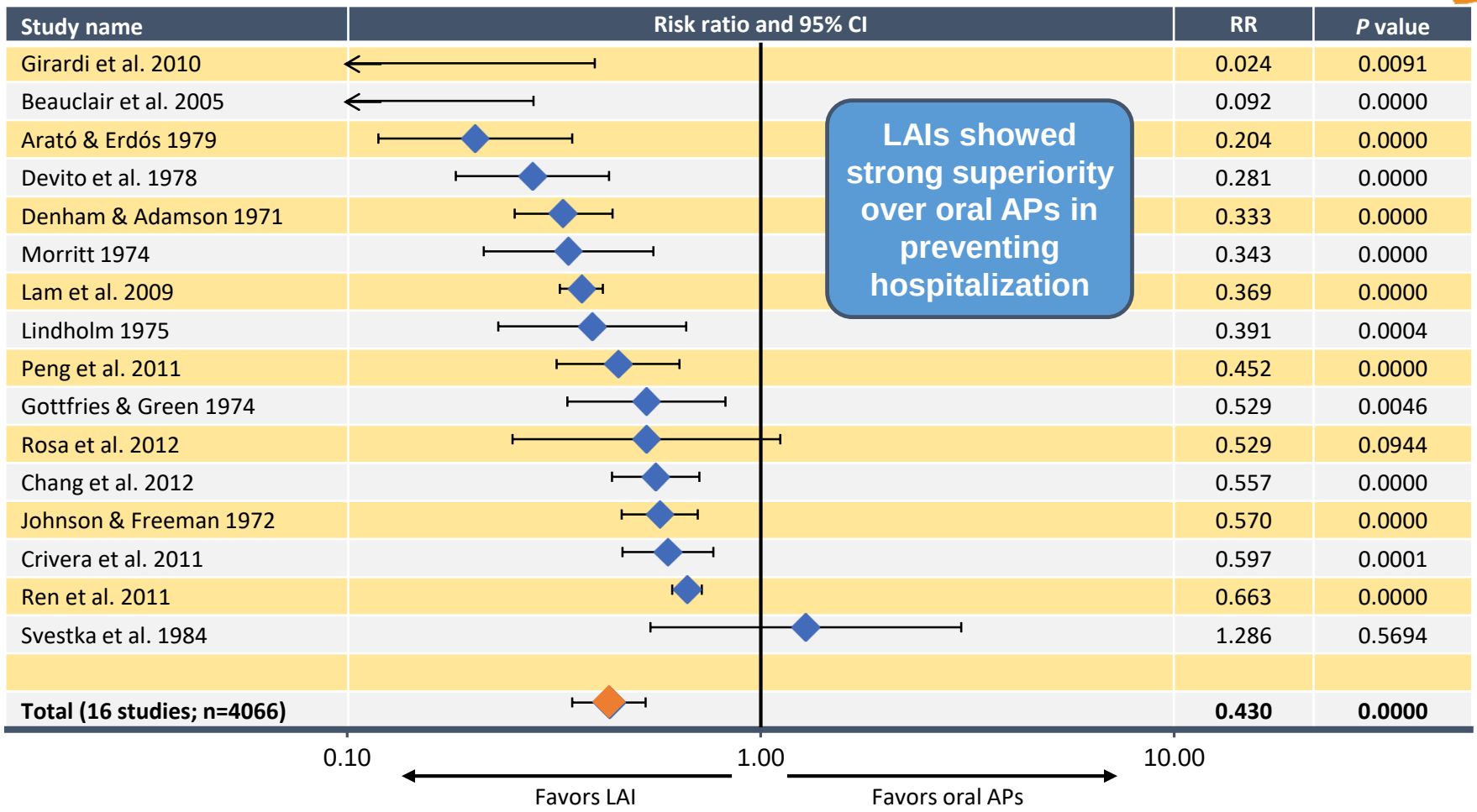
- The next level is drawn on a random day and is close to that expected for the dose. However, he later becomes irritable and a repeat level is quite low.
- **What is the next step ??**

The Rationale for Long-Acting Injectables

WHY USE LONG-ACTING INJECTABLE (LAI) ANTIPSYCHOTICS?

- Adherence is assured
- Stable plasma levels mean equal or increased efficacy and occasionally fewer side effects due to less peak to trough drug level fluctuations
  - **NB:** LAIs do not convert nonresponders into responders. If a patient is treatment resistant, he/she needs clozapine.
- Lack of adherence is rapidly identified; patients don't suffer immediate drop in drug levels

MIRROR-IMAGE LAI STUDIES SHOW REDUCED RISK OF HOSPITALIZATION COMPARED WITH ORALS



AP = antipsychotic; CI = confidence interval; LAI = long-acting injectable antipsychotic; RR = risk ratio.
Kishimoto T, et al. *J Clin Psychiatry*. 2013;74(10):957-965.

REHOSPITALIZATION RISK FOR LAI MEDICATION IS LOWER AFTER FIRST SCHIZOPHRENIA HOSPITALIZATION

Group	Adjusted Hazard Ratio	95% CI	*P*
Any depot vs. equivalent oral	**0.36**	**0.17–0.75**	**0.007**
Haloperidol depot vs. haloperidol oral	0.12	0.01–1.13	0.06
Risperidone depot vs. risperidone oral	0.57	0.30–1.08	0.09

CI = confidence interval.
Tiihonen J, et al. *Am J Psychiatry*. 2011;168(6):603-609.

WHY DON'T WE USE LAI ANTIPSYCHOTICS MORE?

- **Provider issues**
  - 90% of psychiatrists never/rarely recommend an LAI antipsychotic after first episode and only 50% recommend LAIs after multiple relapses[1]
  - Lack of case manager or treatment team emphasis[2]
- **Patient issues**
  - Negative image of injectables[2]
  - Concerns about pain and adverse effects[2]
- **System issues**
  - Cost[2]
  - Personnel/administrative burden [2]

LAI = long-acting injectable antipsychotic.

1. Jaeger M, Rossler W. *Psychiatry Res*. 2010;175(1-2):58-62. 2. Correll CU. http://www.cmeinstitute.com/Psychlopedia/Pages/psychosis/10bbu/default.aspx. Accessed September 3, 2014.

OUR DIVERSION CLIENT – PART 3

The client states that weight gain and sexual dysfunction were the reasons he skipped medication doses.

He understands that medication refusal will end his diversion program participation and agrees to an LAI, but wishes to avoid these side effects.

- There is also history of akathisia and dystonia with typical antipsychotics (haloperidol).

Preparations and Basic Kinetics: Typical Antipsychotics and Olanzapine

Preparation	Diluent	Dosage	T_{max} (days)	Steady State $T_{1/2}$ (days)	Able To Be Loaded
Fluphenazine Decanoate	Sesame Oil	12.5 - 100 mg/ 2 weeks	0.3 - 1.5	14	**Yes**
Haloperidol Decanoate	Sesame Oil	25 - 400 mg/ 4 weeks	3 - 9	21	**Yes**
Olanzapine Pamoate *	Water	150-300 mg/ 2 weeks **OR** 300-405 mg/ 4 weeks	7	30	**Yes**

* After each **olanzapine pamoate** injection, a healthcare professional must continuously observe the patient at the healthcare facility for at least 3 hours.

* Following the 3-hour observation period, healthcare professionals must confirm that the patient is alert, oriented, and absent of any signs and symptoms of post-injection delirium/sedation syndrome prior to being released.

Preparations and Basic Kinetics: Risperidone and Paliperidone

(AKA 9-OH Risperidone)

Preparation	Diluent	Dosage	T_{max} (days)	Steady State $T_{1/2}$ (days)	Able To Be Loaded
Paliperidone Palmitate Monthly	Water	39-234 mg/ 4 weeks	13	25 - 49	**Yes**
Paliperidone Palmitate 3-month	Water	273-819 mg/ 12 weeks	30-33	84 - 95 (deltoid) 118 - 139 (gluteal)	No
Risperidone Microspheres	Water	12.5-50 mg/ 2 weeks	21	3 - 6	No
Risperidone Sucutaneous	**Water**	**90-120 mg/ 4 weeks**	**4-6 hrs (1st peak) 8 days (2nd peak)**	**9- 11**	**Not necessary**

Tmax = time to maximum plasma level

Preparations and Basic Kinetics: Aripiprazole

Preparation	Diluent	Dosage	T_{max} (days)	Steady State $T_{1/2}$ (days)	Able To Be Loaded
Aripiprazole Monohydrate	Water	300-400 mg/4 weeks	6.5 - 7.1	29.9 – 46.5	No *
Aripiprazole Lauroxil	**Water**	**441-882 mg/4 weeks 882 mg/6 weeks 1064/8 weeks**	**41 (single dosing) 6 – 21 (multiple dosing)**	**53.9 – 57.2**	**No ****
Aripiprazole Lauroxil Nanocrystal	**Water**	**675 mg once**	**27 (range 16-35)**	**15-18 (single dose)**	**Only for initiation or resumption**

* Start therapy with 14 days oral overlap

** Start therapy with one aripiprazole lauroxil nanocrystal injection + a single 30 mg oral dose in addition to the clinician determined dose of aripiprazole lauroxil.

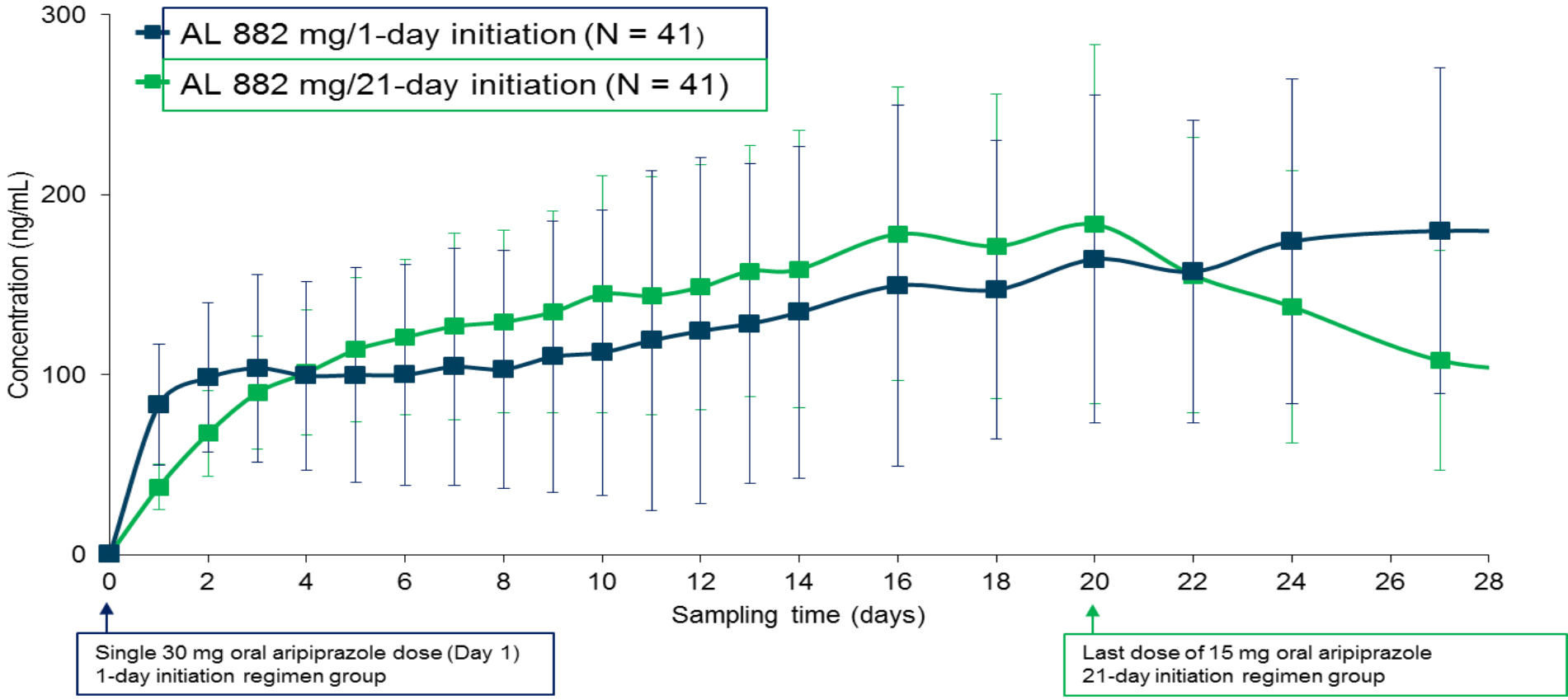
ARIPIPRAZOLE LAUROXIL (AL) NANOCRYSTAL DISPERSION

- A 1-day regimen involving a single 675 mg injection of the nanocrystal AL ***AND*** one 30 mg oral aripiprazole dose. This provides aripiprazole levels comparable to the old 21-day oral coverage regimen.
- Patients also receive a maintenance injection of aripiprazole lauroxil at the same time. Due to the long onset of action, this does not contribute significantly during the first weeks of treatment.
  - The maintenance AL dose is chosen depending on the patient's need for medication. Options include:

882 mg/4wks	**= 20 mg/d oral aripiprazole**
662 mg/4 wks or 882 mg/6 wks	**= 15 mg/d oral aripiprazole**
1064 mg/8 wks	**≤ 15 mg/d oral aripiprazole**
441 mg/4 wks	**= 10 mg/d oral aripiprazole**

Meyer JM. Aripiprazole lauroxil nanocrystal suspension. *Current Psychiatry*. 2018;17:34-40.

DRUG LEVELS WITH ONE DAY METHOD VS 21 DAYS OF ORAL ARIPIPRAZOLE (15 MG/D)



Meyer JM. Aripiprazole lauroxil nanocrystal suspension. *Current Psychiatry*. 2018;17:34-40.

PRN Meds in the Community

OUR DIVERSION CLIENT – PART 4

The client agrees to an LAI form of aripiprazole mostly to avoid side effects concerns such as weight gain, sexual dysfunction, and prior history of sensitivity to typical antipsychotics.

He does well on AL 1064 mg/8 weeks over the next few months, but every few weeks has a 48 hour period where he appears ‘spaced out’ and more symptomatic, and was verbally belligerent on one occasion. UDS is negative during these episodes, but hallucinogen use is suspected.

The staff ask for a PRN prescription to avert calling the police unless absolutely necessary.

What are the options?

PRN MEDICATIONS IN DIVERSION

Where possible, use of PRN antipsychotics can be helpful to avert rehospitalization or other behaviors that can end program participation

- Benzodiazepines and other sedatives must not be used for agitation or psychotic exacerbations due to the weak efficacy data and high abuse liability in this population

Options

a. **Oral dissolving tablets or liquid oral suspensions**
b. **Inhaled loxapine (under new proposed FDA rules)**
c. **Intranasal olanzapine (if approved)**

ORAL ANTIPSYCHOTIC SOLUTIONS

Antipsychotic (concentration)	**Tmax**
Haloperidol lactate oral solution (2 mg/ml)	2-6 hrs
Fluphenazine oral concentrate (5 mg/ml)	2.4 hrs
Loxapine oral concentrate (25 mg/ml)	**1-2 hrs**
Aripiprazole oral solution (1 mg/ml)	3-5 hrs
Risperidone oral solution (1 mg/ml)	**1 hr (Risp)**
	3-17 hrs (9-OH Risp)

Issues: Must be mixed in compatible solution (e.g. for loxapine this is orange or grapefruit juice)

Benefits: The oral concentrate is not absorbed any faster than tablets, but is likely to stay in the GI tract and be absorbed.

ORAL DISSOLVING TABLETS (ODT)

- Tablets can be easily cheeked
- ODT stick like cotton candy and cannot be easily cheeked and spat out

Options

Aripiprazole ODT: 10, 15 mg

- Tmax – 3-5 hrs

Risperidone ODT: 0.5, 1, 2, 3, 4 mg

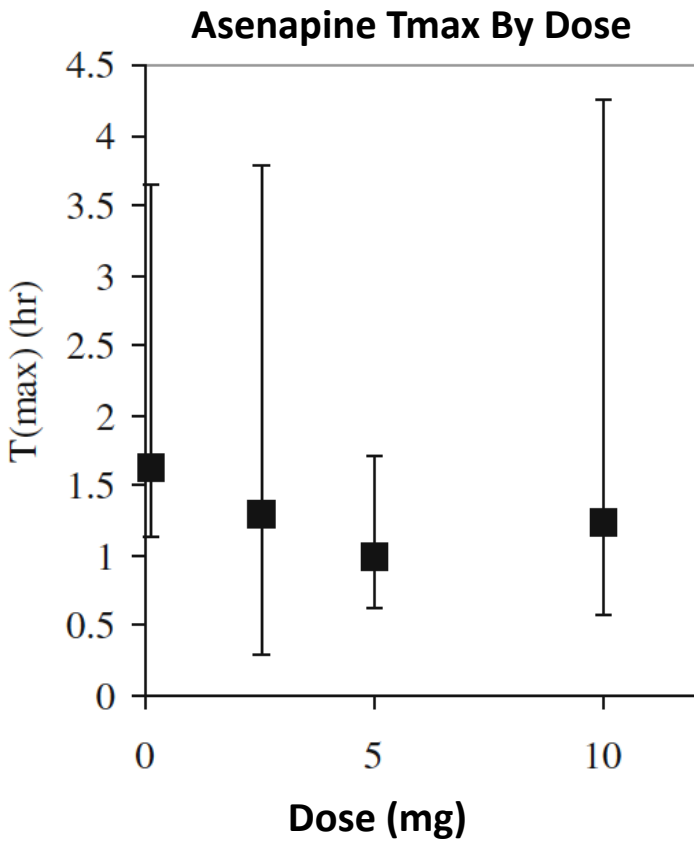
- **Tmax – Risp 1 hr; 9-OH Risp 3-17 hrs**

Olanzapine ODT: 5, 10, 15, 20 mg

- Tmax – 6 hrs

Asenapine ODT: 2.5, 5, 10 mg

- **Tmax – 1 hour**



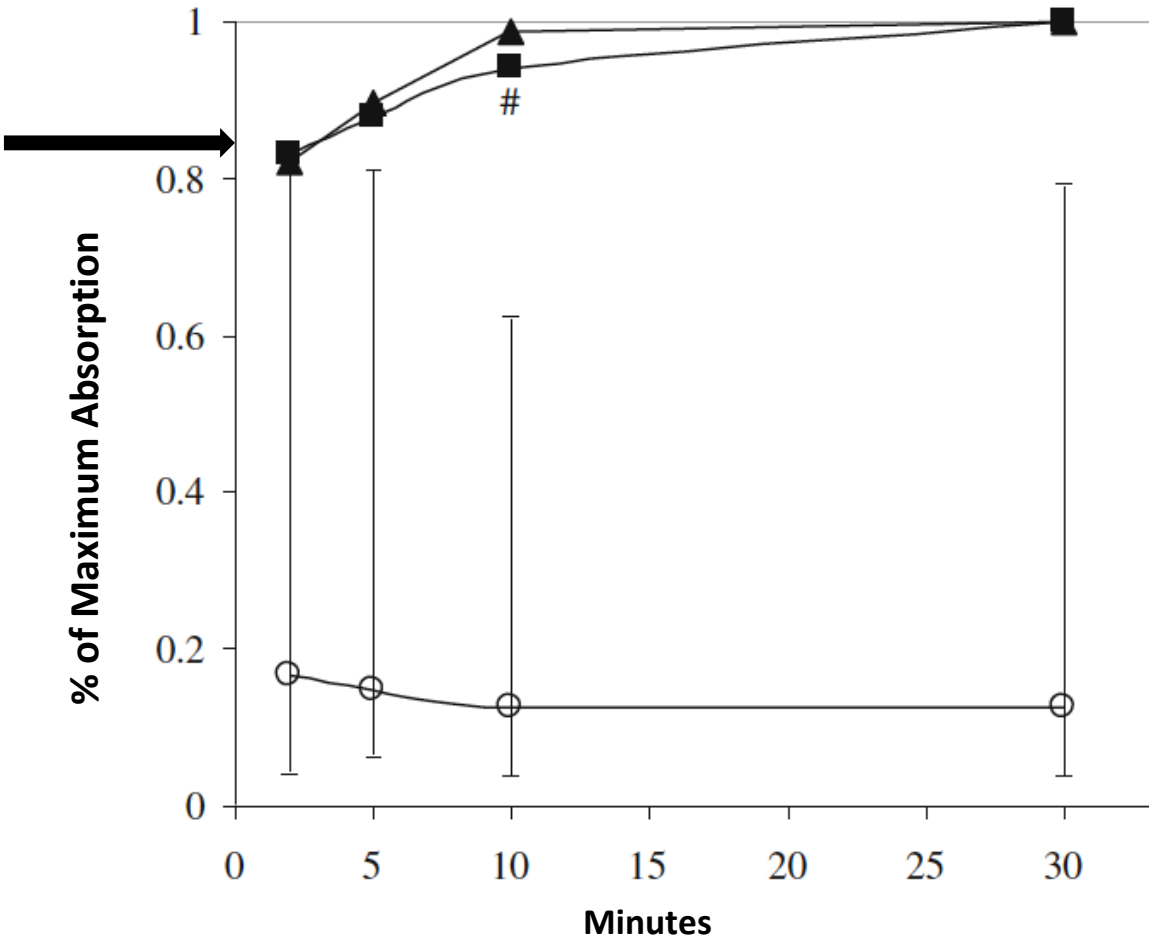
Bartlett JA, et al. Understanding the Oral Mucosal Absorption and Resulting Clinical Pharmacokinetics of Asenapine. AAPS PharmSciTech 2012; 13(4):1110-1115

ASENAPINE (ODT) – PRACTICAL ISSUES

- All of the drug absorption occurs within the mouth (i.e. oral mucosa). If the patient drinks water immediately and swallows the medication, 98% of it is metabolized and ***gone.***
- How to administer:
  - **Wafer is placed under the tongue to avoid unpleasant taste and weird tongue numbness. The 10 mg dose is preferable.**
  - **Maximum absorption (32% - 35%) of the dose is achieved if no water is ingested for 10 minutes.**
  - **However, if one keeps the patient away from water for 2 minutes, you'll get 80% of the maximum absorption.**

Bartlett JA, et al. Understanding the Oral Mucosal Absorption and Resulting Clinical Pharmacokinetics of Asenapine. AAPS PharmSciTech 2012; 13(4):1110-1115

ASENAPINE (ODT) – AVOIDING WATER FOR 2 MIN GETS 80% OF MAXIMUM POSSIBLE ABOSPRTION



Bartlett JA, et al. AAPS PharmSciTech 2012; 13(4):1110-1115

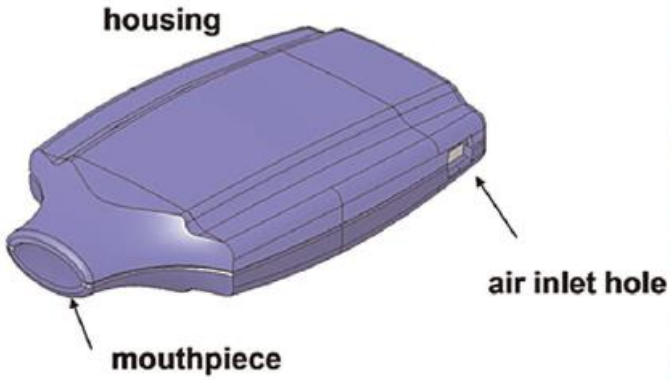
ADASUVE (INHALED LOXAPINE)

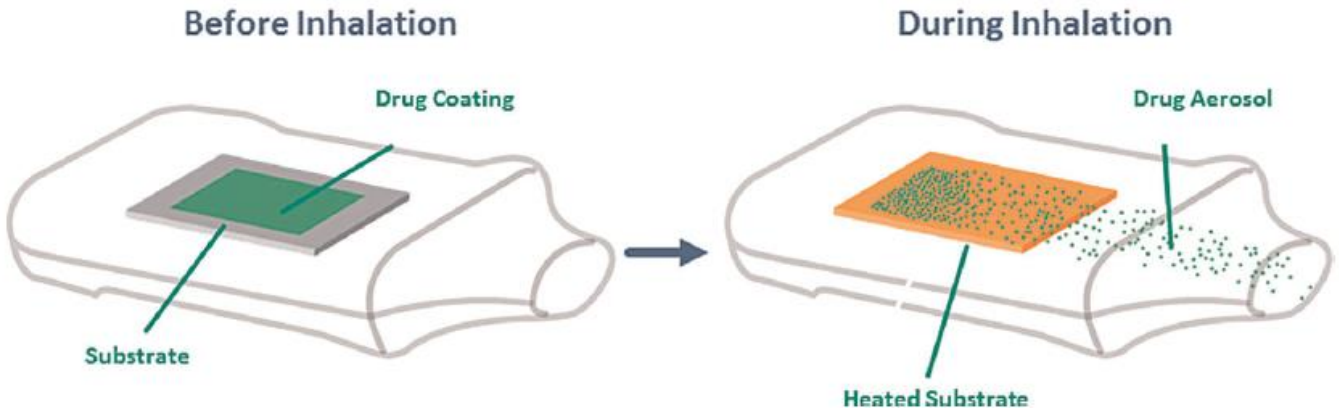
- Loxapine is a typical antipsychotic available since 02/25/1975
- Inhaled 10 mg version for acute treatment of agitation in schizophrenia or bipolar I disorder approved 12/21/2012
- Due to bronchospasm concerns, a **Risk Evaluation and Mitigation Strategy** (REMS) program was required by FDA:

  "Adasuve can cause bronchospasm that has the potential to lead to respiratory distress and respiratory arrest. Administer Adasuve only in an enrolled healthcare facility that has immediate access on site to supplies and personnel trained to manage acute bronchospasm and ready access to emergency response services [see Warnings and Precautions (5.1, 5.2)]."
- **New submission before FDA to make Adasuve available to any patient who has a bronchodilator (inhaler) available if needed.**

1. Spyker DA, et al. Multiple Dose Pharmacokinetics of Inhaled Loxapine in Subjects on Chronic, Stable Antipsychotic Regimens. J Clin Pharmacology 2015; 55(9): 985–994.
2. Alexza Pharmaceuticals, Inc. Adasuve Package Insert Feb 2017.

ADASUVE (INHALED LOXAPINE)





Spyker DA, et al. Multiple Dose Pharmacokinetics of Inhaled Loxapine in Subjects on Chronic, Stable Antipsychotic Regimens. J Clin Pharmacology 2015; 55(9): 985–994.

IMPEL INP105 (OLANZAPINE NASAL SPRAY)

- Olanzapine is an atypical antipsychotic available since 09/30/1996
- Metered, propellant powered nasal delivery system has been developed by Impel to deliver a number of meds – olanzapine is targeted for acute agitation in schizophrenia and bipolar I
- The nasal delivery system with INP105 gets drug to the upper nasal cavity. Olanzapine reaches peak plasma levels twice as fast as intramuscular olanzapine, and 10 times faster than orally-disintegrating tablets (ODT).

1. Shrewsbury SB, et al. Placebo/Active Controlled, Safety, Pharmaco-Kinetic/Dynamic Study of INP105 (POD® olanzapine) in Healthy Adults. Western Journal of Emergency Medicine: Integrating Emergency Care with Population Health 2019; 20(2)

IMPEL INP105 (OLANZAPINE NASAL SPRAY)

1. Liquid drug from the vial enters the drug holding chamber
2. In same actuation step, liquid HFA propellant is metered to the drug holding chamber
3. HFA is converted to gas and pushes dose out of nozzle
4. Narrow precision stream of drug is driven by HFA gas to the deep nasal cavity

How it Works

1. Shrewsbury SB, et al. Placebo/Active Controlled, Safety, Pharmaco-Kinetic/Dynamic Study of INP105 (POD® olanzapine) in Healthy Adults. Western Journal of Emergency Medicine: Integrating Emergency Care with Population Health 2019; 20(2)

CONCLUSIONS

- Nonadherence is common among schizophrenia patients. Measures have to be in place to monitor adherence.
- For those on oral medications dose is a poor predictor of plasma level due to adherence and kinetic issues
  - Obtaining repeated plasma levels can help detect nonadherence
  - A working knowledge of dose-plasma level relationships for oral antipsychotics can help detect adherence issues
- Long-acting injectable antipsychotics must be used when oral medication nonadherence occurs
  - Choice of medication depends on prior history of response and tolerability
  - Once adherence has been removed from the equation, one can better determine if a patient is treatment resistant and needs clozapine
- PRN options in the community include dissolving antipsychotic tablets, solutions and possibly inhaled loxapine or intranasal olanzapine.

QUESTIONS?